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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/002,796 | 11/15/2001 | Avi J. Ashkenazi | P3130R1C1 | 5287 |

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Attn: Ginger R. Dreger, Esq.
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| EXAMINER | |
|---|---|
| CHERNYSHEV, OLGA N | |
| **ART UNIT** | **PAPER NUMBER** |
| 1646 | |

DATE MAILED: 04/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/002,796 | ASHKENAZI ET AL. | |
| | Examiner | Art Unit | |
| | Olga N. Chernyshev | 1646 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *26 March 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *40-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of the claims*

1. Claims 1-39 have been cancelled and claims 40-52 have been added as requested in the amendment submitted on March 26, 2002. Claims 40-52 are pending in the instant application.

Claims 40-52 are under examination in the instant office action.

### *Specification*

2. The use of the trademarks has been noted in this application, see page 148, line 8, for example. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Applicant is advised to review the entire text of the instant specification for other possible use of trademarks.

### *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3. Claims 40-52 are rejected under 35 U.S.C. 101 because the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility. The instant application has provided a description of an isolated DNA encoding a protein and the protein

encoded thereby. The instant application does not disclose a specific biological role for this protein or its significance to a particular disease, disorder or physiological process, which one would wish to manipulate for a desired clinical effect.

It is clear from the instant application that the protein described therein is what is termed an "orphan protein" in the art. The DNA of the instant application has been isolated because of its similarity to a known DNA. There is little doubt that, after complete characterization, this DNA and encoded protein may be found to have a specific and substantial credible utility. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediate obvious or fully disclosed "real world" utility. The court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion".

The instant claims are drawn to an isolated polypeptide of SEQ ID NO: 9 of as yet undetermined function or biological significance. It is clear from the instant specification that

the claimed novel polypeptide designated PRO444 is a secreted protein (page 3, lines 2-6 of the instant specification) that is encoded by a cDNA "DNA 26846-1397" of SEQ ID NO: 8 (page 27, lines 5-9), which "was isolated from a human fetal lung library using a trapping technique which selects for nucleotide sequences encoding secreted proteins" (page 65, lines 26-31). Clone DNA 26846-1397 was deposited with the ATCC and assigned number 203406 (page 104, lines 14-15). The research data presented in the instant specification indicate that PRO444 of SEQ ID NO: 9 induced the expression of c-fos in pericyte cells (page 142, Example 60). Based on the results of the assay disclosed in the Example 60 it was asserted that the instant PRO444 polypeptides "are useful not only as diagnostic markers for particular types of pericyte-associated tumors but also for giving rise to antagonists which would be expected to be useful for the therapeutic treatment of pericyte-associated tumors" (bottom at page 142). However, it is well described in the art that induction of c-fos expression represents a general cellular response to a variety of stimuli. The *c-fos* proto-oncogene is a member of the immediate-early genes (IEGs) which are rapidly induced upon stimulation of cells with growth factors, cytokines, serum or UV-light (see Janknecht et al, 1995, Introduction and p. 444, for example). In the central nervous system *c-fos* activation has been demonstrated to be induced by neurotropic factors, neurotransmitters, depolarizing agents or ion channel activating agents (Herrera et al., 1996, p. 84, first column and p. 86, second column and also Kovacs, 1998, p. 289, Mechanism of fos induction). It is summarized in Kovacs article that "[s]tereotypic inducibility of c-fos proto-oncogene rendered this cellular immediate-early gene (IEG) to be the most widely used functional anatomical mapping tool to identify cells and extended circuitries that became activated in response to various stimuli" (page 287, first column). Thus, according to the state of

the art, activation of c-fos appears to be a non-specific first line of cellular response and, therefore, one skilled in the art would readily conclude that activation of c-fos could not support the assertion of specific and substantial credible utility of PRO444 "as diagnostic marker[s] for particular types of pericyte-associated tumors". Moreover, because the instant specification fails to identify any particular type of tumor that the instant PRO444 is specifically associated with, the assertion of specific utility of PRO444 polypeptides as cancer markers appears to be not supported by any evidence of record.

In the absence of knowledge of the biological significance of this specific PRO444 protein, there is no immediately obvious patentable use for it. According to the specification of the instant application "[I]nductionof c-fos expression in pericytes is also indicative of the induction of angiogenesis and, as such, PRO [444] polypeptides capable of inducing the expression of c-fos would be expected to be useful for the treatment of conditions where induced angiogenesis would be beneficial, for example, wound healing, and the like" (page 142, lines 24-27 of the instant specification). The instant specification fails to provide any evidence or sound scientific reasoning that would support a conclusion that the instant PRO444 protein is specifically associated with angiogenesis. Because c-fos activation represents a non-specific cellular response that generally reflects the functional activity of a cell (see reasons of record earlier in this section), one would have no reasons to conclude that upregulated expression of c-fos after treatment of pericytes with PRO444 polypeptide supports the use of PRO444 polypeptides in wound healing.

Furthermore, to employ the instant PRO444 protein in the methods for generation of antibodies or diagnostic assays is not a "real world" utility because it would eventually relate to a

protein for which no biological function is known. Because the instant specification does not teach a biological activity of the PRO444 protein, which supports a practical utility, one would not reasonably believe that the administration of the claimed peptide would prevent or treat a condition or disease, like pericyte-associated tumors or wound healing, as implied by the specification. To employ a polypeptide PRO444 of the instant invention in any of the disclosed methods would clearly be using it as the object of further research, which has been determined by the courts to be a utility, which, alone, does not support patentability. Since the instant specification does not disclose a substantial "real world" use for the PRO444 protein in their currently available form, then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. § 101 as being useful.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 40-52 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a clear asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

5. Claims 40-44 and 51-52 are further rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 40-44 are directed to polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity with a polypeptide of SEQ ID NO: 9. Claims 51-52 are dependent claims. The claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides that is defined only by sequence identity. However, the instant specification fails to describe the entire genus of proteins, which are encompassed by these claims. In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicant has possession of and what Applicant is claiming. From the specification, it is clear that Applicant has possession of a nucleic acid molecule which encodes a protein which has the amino acid sequence of SEQ ID NO: 9. This nucleic acid molecule has a nucleic acid sequence of SEQ ID NO: 8 and is contained within ATCC deposit number 203406AA. The claims are drawn to proteins having at least 80%, 85%, 90%, 95% or 99% sequence identity with a particular disclosed sequence. Thus, the claims are not limited to a protein with a specific amino acid sequence. The claims only require the claimed polypeptides to share some degree of structural similarity to the isolated protein of SEQ ID NO: 9. However, the specification only describes a polypeptide having the amino acid sequence of SEQ ID NO: 9 and fails to teach or describe any other polypeptide which lacks the amino acid sequence of SEQ ID NO: 9 and has the activities possessed by the isolated protein.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. The specification does not provide a complete structure of those polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity with a polypeptide of SEQ ID NO: 9 and fails to provide a representative number of species for the claimed genus (those proteins having at least 80%, 85%, 90%, 95% or 99% sequence identity with a polypeptide of SEQ ID NO: 9). Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of

the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 9, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 40-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claims 40-45, 48 and 49 are vague and indefinite for recitation of "extracellular domain" claimed to be shown in Figure 4. However, Figure 4 does not indicate the claimed sequences. Clarification is required.

8. Claims 46-47 and 50-51 are indefinite for being dependent from indefinite claims.

***Conclusion***

9. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Olga N. Chernyshev whose telephone number is (571) 272-0870. The examiner can normally be reached on Monday to Friday 9 AM to 5 PM ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (571) 272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)0. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 872-9306. If this number is out of service, please call the Group receptionist for an alternative number. Faxed draft or informal communications with the examiner should be directed to (571) 273-0870. Official papers should NOT be faxed to (571) 273-0870.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Olga N. Chernyshev, Ph.D.

OLGA N. CHERNYSHEV, PH.D.
PATENT EXAMINER